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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
DARIO CREMASCHI, ET AL. : EXAMINER: NICKOL, G.B.
SERIAL NO: 09/988,150 :
FILED: NOVEMBER 19, 2001 : GROUP ART UNIT: 1642
FOR: USE OF MICROPARTICLES :
HAVING A PROTEIN AND AN
ANTIBODY ADSORBED THEREON FOR
PREPARING A PHARMACEUTICAL
COMPOSITION FOR INTRANASAL
ADMINISTRATION

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This brief is submitted in response to the final rejection dated April 9, 2004.

REAL PARTY OF INTEREST

The real party of interest herein is Aziende Chimiche Riunite Angelini Francesco

A.C.R.A.F. S.p.A, of Roma, Italy.

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RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 11-13, 15-22, and 24-28 are pending. Claims 20-22 and 24-28 have been indicated as being allowable in the final Office Action dated April 9, 2004. Claims 11-13 and 15-19 are rejected.

STATUS OF AMENDMENTS

An amendment after final was submitted on August 2, 2004. Those amendments were not entered and therefore, the claims appealed herein are the claims of record entered and considered prior to the final Office Action of April 9, 2004.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is to a method for intranasally administering a composition comprising a microparticle having a protein and an antibody specific for the protein adsorbed thereon, by contacting a microparticle having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof.

This method provides an efficient means of presenting the microparticles to a patient and yield significantly better results than methods previously employed. Significantly, as described on page 4, line 4 of the present specification, the claimed method provides 400,000 times higher levels than administration in the intestine.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The sole rejection to be reviewed on appeal is of Claims 11-13 and 15-19 under 35 U.S.C. § 103 in view of Smith et al (WO94/28879) and Almeida et al (J. Drug Targeting, 1996, vol. 3, pages 455-467).

ARGUMENT

The claimed invention is not obvious for two reasons. First, the combination of Smith and Almeida do not provide the requisite motivation to perform the claimed method, i.e., intranasal administration of the composition defined in Claim 11. Second, the combination of cited prior art provide no suggestion or reasonable expectation for the vast improvement for the delivery of the composition defined in Claim 11 when delivered through the nasal mucosa relative to the intestinal mucosa, which data are of record in the present application. These points are further elaborated upon in the remarks below with reference to the cited prior art and the present specification.

Smith is described in the present specification on page 2, last paragraph. Smith describes a composition of a protein and an antibody absorbed on a microparticle (page 736, last paragraph). Smith describes administering this composition to the intestine (see “Summary” on page 735, “Experimental” on page 736, “Microsphere uptake by intestinal M cells” on page 737, and “Discussion” on pages 741-742). Smith does not describe intranasal administration.

For intranasal administration, the Office has cited Almeida and has alleged that one would employ the Smith composition intranasally based on the suggested advantages of nasal delivery in Almeida (page 457, col. 1). Appellants disagree.

The combined teachings of the cited references do not suggest the present method of intranasal administration and as such fail to support a *prima facie* case of obviousness. In particular, while Almeida, on page 457, col. 1, describes several advantages of administering drugs nasally, a further reading of Almeida reveals the following on page 471, second column, second paragraph (emphasis added):

The mode of entry of nasally administered particles into the circulation is not fully understood and few investigators have postulated putative mechanisms (Kuper et al., 1992). The nasal adsorption of fluorescent polystyrene particles has been observed, which suggests that the mechanism of solid particle uptake by the nasal mucosa is similar to that found in the gut (Alpar et al., 1994).

Thus, while Almeida generally describes drugs on page 457, when Almeida specifically discusses the administration of particles, the claimed invention employs microparticles, Almedia suggests that absorption to through the intestinal and nasal mucosa are similar. Therefore, the motivation to administer the Smith composition intranasally is based either on hindsight reconstruction of the present invention or under an obvious to try rationale, both of which are improper for establishing that the claimed invention would have been obvious.

It is further noted, "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combinations".¹ The Patent Office can only satisfy its burden to establish a *prima facie* case of obviousness "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to

¹ In re Geiger, 815 F.2d 686, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987).

combine the relevant teachings of the references."² For the reasons set forth above, such teachings, suggestions or incentives are missing here.

In any case, even a *prima facie* case is rebutted by the data of record in the application which demonstrates greater than 400,000 times more microparticles absorbed through the nasal mucosa compared to the intestines. In particular, Appellants note the Office's guidelines for examination set forth in MPEP § 716.02(a): "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985).

The data are presented on pages 3, 4 and 11 of the present specification are summarized below:

(1) In the intestine: $\text{yield}/\text{cm}^2 = 4.4 \times 10^{-9}$ (=0.0000044°/oo) - page 3, line 28

(2) In the nasal mucosa: $\text{yield}/\text{cm}^2 = 1.7 \times 10^{-3}$ (=1.7°/oo) which is 400,000 times greater than the absorption in the intestine - page 11, lines 22-28.

As has been previously discussed, the comparisons provided in the specification performed *in vivo* at 37°C and the experiments performed for the nasal mucosa performed *in vitro* at 27°C are comparable and provide the following in support of this assertion.

As discussed on page 9, lines 25 to 27: "The incubation temperature was 27°C ± 1°C. As compared with 37°C, this temperature lowers metabolism and transport twice as much, but renders the isolated tissue more stable." Since microparticle transport at 27°C is 400,000 times greater than transport in the intestine at 37°C (page 11, lines 22-28), it would be expected that if the experiments in the nasal mucosa were performed at 37°C the resulting increase through the nasal mucosa would have been approximately 800,000 times greater than the intestine. Clearly, this result is even more dramatic and is greater than an expected

² *In re Fine*, 837 F.2d 1071, 5 USPQ 2d 1596, 1598 (Fed. Cir. 1988).

result. Additionally, it is noted that since the nasal mucosa (nostril) is exposed and not as well insulated by the body (compared to an internal organ such as the intestine), the temperature of the nasal mucosa is more susceptible to changes in the ambient temperature. For example, if the ambient temperature is approximately 22°C, the temperature of the nostril would be approximately 32°C and as the ambient temperature declines, the nostril temperature will also decline. Thus, the experimental conditions of 27°C more closely mimics the real temperature of the nasal mucosa in a living individual.

Turning to the issue comparing *in vitro* testing and *in vivo* testing, the comparison of *in vivo* intestinal data and *in vitro* nasal mucosa data is appropriate. Intestinal tissue isolated for *in vitro* testing consists of mono-layered epithelium, a layer of connective tissue underneath (which contains the ducts and thick lymphoid tissue of the Peyer's patches), two layers of musculature, another layer of connective tissue and a serous membrane. *In vivo* the proteins are adsorbed by intestinal epithelium, then pass into connective tissue where they then reach the ducts and where the microparticle numbers are measured (see page 3, lines 20-23). Contrast this adsorption pathway to the adsorption *in vitro*, where the proteins have to pass through the whole wall of the isolated intestine before being measured and thus much of the proteins to be measured are lost. Accordingly, the absorption of proteins in the intestine is significantly more efficient *in vivo* than *in vitro*. The nasal mucosa membranes isolated for *in vitro* testing consists of a psuedoepithelium layer and a thin layer of connective tissue. Thus, the adsorbed protein passes through the nasal mucosa in much the same way both *in vitro* and *in vivo*, *in vivo* the protein reaches the ducts whereas *in vitro* the protein passes through the thin layer connective tissue.

Accordingly, comparing transport in the nasal mucosa *in vitro* at 27°C with the transport in the intestine *in vivo* at 37°C is physiologically more correct than comparing transport of the two tissues both *in vitro* or *in vivo* at the same temperature.

It is submitted in view of the foregoing that the claimed invention, in Claims 11-13 and 15-19, are not obvious in view of the combined teachings of the cited references since the references fail to suggest this claimed method and the significant absorption of the microparticle composition in the nasal mucosa when compared to the absorption of the same microparticle composition in the intestine.

Accordingly, in view of the above remarks and reasons explaining the patentable distinctness of the presently appealed claims over the applied prior art, Appellants request that the Examiner's rejections be REVERSED.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

Customer Number
22850



Daniel J. Pereira, Ph.D.
Registration No. 45,518

APPENDIX 1 (CLAIMS)

Claims 1-10 (Cancelled).

11. (Rejected) A method for intranasally administering a composition comprising a microparticle having a protein and an antibody adsorbed thereon, wherein said administering comprises contacting a microparticle having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof, wherein said antibody is an immunoglobulin specific for the protein.

12. (Rejected) The method of Claim 11, wherein said protein is selected from the group consisting of BSA, insulin, enkephalin, hormones, growth factors, cytokines, coagulation factors, polypeptides, and antimicrobial agents.

13. (Rejected) The method of Claim 11, wherein said antibody is an immunoglobulin selected from the group consisting of IgM, IgA, and IgG.

Claim 14 (Cancelled).

15. (Rejected) The method of Claim 11, wherein said microparticle is biodegradable.

16. (Rejected) The method of Claim 11, wherein said microparticle comprises polystyrene.

17. (Rejected) The method of Claim 11, wherein the ratio of protein to antibody is 1 to 15,000 moles of protein per mole of antibody.

18. (Rejected) The method of Claim 11, wherein the ratio of protein to antibody is 1 to 5,000 moles of protein per mole of antibody.

19. (Rejected) The method of Claim 11, wherein the ratio of protein to antibody is 1 to 100 moles of protein per mole of antibody.

20. (Allowed) A method for intranasally administering a composition comprising a microparticle and an antibody adsorbed thereon, wherein said administering comprises having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof, and wherein the transepithelial transport obtained with 3.2×10^{11} microparticles/ml is 1.7% , wherein said antibody is an immunoglobulin specific for the protein.

21. (Allowed) The method of Claim 20, wherein said protein is selected from the group consisting of BSA, insulin, enkephalin, hormones, growth factors, cytokines, coagulation factors, polypeptides, antimicrobial agents.

22. (Allowed) The method of Claim 20, wherein said antibody is an immunoglobulin selected from the group consisting of IgM, IgA, and IgG.

Claim 23 (Cancelled).

24. (Allowed) The method of Claim 20, wherein said microparticle is biodegradable.

25. (Allowed) The method of Claim 20, wherein said microparticle comprises polystyrene.

26. (Allowed) The method of Claim 20, wherein the ratio of protein to antibody is 1 to 15,000 moles of protein per mole of antibody.

27. (Allowed) The method of Claim 20, wherein the ratio of protein to antibody is 1 to 5,000 moles of protein per mole of antibody.

28. (Allowed) The method of Claim 20, wherein the ratio of protein to antibody is 1 to 100 moles of protein per mole of antibody.

APPENDIX II (EVIDENCE)

None.